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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/644,289	05/10/96	KULESZ-MARTIN M	RPF:135D-US

18M1/1015

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EXAMINER	
EYLER, Y	
ART UNIT	**PAPER NUMBER**
1806	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/644,289	Applicant(s) Kulesz-Martin
	Examiner Yvonne Eyler	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Jul 7, 1997* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-6, and 8-15* is/are pending in the application.

Of the above, claim(s) *12-14* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-6, 8-11, and 15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-11 and 15 in Paper No. 8 is acknowledged.

Claims 1, 3-6, and 8-15 are pending in the application. Claims 12-14 are withdrawn from consideration as being drawn to a non-elected invention.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The objections to the disclosure are withdrawn, however, it is noted that only allowed applications and applications linked to allowed applications are obtainable from the U.S.P.T.O. Abandoned (as in the instant case) and pending applications are not available.

Claim Rejections Withdrawn:

4. The rejection of Claims 2 and 7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of their cancellation.

5. The rejection of Claims 2 and 7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

6. The rejection of Claim 2 under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) is withdrawn.

7. The rejection of Claim 2 under 35 U.S.C. 102(b) as being anticipated by Han et al (IDS; Nuc.Acids Res. 20:1979-1981, 1992) is withdrawn.

8. The rejection of Claim 7 under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (Mol. Cell Biol. 5:127-132, 1985), Han et al (Nuc.Acids Res. 20:1979-1981, 1992), or Arai et al (Mol. Cell Biol. 6:3232-3239, 1986) in view of Lee et al (IDS; EP 529160) is withdrawn.

Claim Rejections Maintained and New Grounds of Rejection:

9. Claims 1, 3-6, 8-11 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 1, 3-6, and 8-11 over the indefiniteness of the designation p53as is withdrawn in light of the amendment to the claims, however, the newly added recitation "functionally equivalent" found in claims 1 and 5 is vague and indefinite because the metes and bounds of the limitation cannot be determined. It is not clear what properties of p53 are considered to be functional. Further, it is not clear what "active" p53 versus "non-active" p53 are and how they differ. Finally, it is not clear what is meant by being functionally equivalent to active

p53 encoded with intron 10. Does this mean that the p53As is encoded without intron 10? Is this meant to indicate that Claims 3, 6, 8-11, and 15 do not overcome this.

The rejection of claim 15 is maintained. Claim 15 is vague and indefinite in the recitation "at least a unique part of SLRPFKALVREKGHRPSHSC, SEQ ID NO. 1." The metes and bound of the claim cannot be determined because the boundaries of "at least a unique part" are not defined.

The addition of Sequence ID numbers is acknowledged and overcomes that basis of rejection with regard to claim 15.

10. Amended Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There appears to be no support in the specification of the recitation "active p53 encoded with intron 10."

There also appears to be no support for differences within the 50 carboxy terminal amino acids which "inactivate" a negative regulatory domain. There is support for p53as which "**lacks**" the negative regulatory domain.

There appears to be no support in the specification for the claim language "so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only."

11. The rejection of Claims 1, 3-6, 8-11 and 15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicants arguments have been considered but are not found to be persuasive. Applicants arguments do not seem to be commensurate with the amount of description and guidance provided in the instant specification. Applicant argues that one would be enabled to take any C-terminally modified protein as taught by Hupp et al and render it immunologically detectable by adding a unique epitope to the C-terminal end. No where is this contemplated or described in the instant specification. The instant specification describes an alternatively spliced p53 molecule which is distinguishable from normal p53 in its C-terminal region. The alternatively spliced molecule is taught to lack the negative regulatory region and have 17 unique amino acids from intron 10. Plasmids containing either full length p53 with the normal C-terminus or plasmids containing full length alternatively spliced p53 with the alternative C-terminus are taught and used to express and characterize the p53as molecule. No description or guidance is provided for generating any other p53 molecules or for tagging any other p53 molecules with a unique epitope. It is maintained that the only p53as molecule which the instant specification provides adequate guidance for and describes is a full length p53 molecule up to nt 1028 followed by the disclosed modified C-terminus of 17 amino acids defined by Seq Id. No. 1, i.e. alternatively spliced p53. There is no further guidance within the instant specification for what other modifications, besides

the instantly disclosed truncation and addition of intron 10 sequence of seq. Id. No. 1, result in the loss of the negative regulatory region. As made of record, the breadth of the changes which are encompassed by the claim language is not commensurate in scope with the description and guidance provided by the instant specification. The amendments to the claims do not remedy this as the claims are still drawn to any p53 molecule which differs in any way from active (wildtype?) p53 in the 50 C-terminal amino acids and has a unique (undefined) epitope anywhere within the molecule for which it would require undue experimentation for one of skill in the art to make or use for the reasons of record and as discussed above.

12. The rejection of Claims 1, 3, and 4 under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) is maintained as evidenced by Arai et al.

13. The rejection of Claims 1, 3, and 4 under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) is maintained as evidenced by Arai et al is newly applied to claim 15 which was inadvertently omitted from the original rejection.

14. The rejection of Claims 1,3, 4 and 15 under 35 U.S.C. 102(b) as being anticipated by Arai et al (IDS; Mol. Cell Biol. 6:3232-3239, 1986) is maintained.

Applicants arguments with regard to Wolf et al and Arai et al will be addressed together.

Applicant argues that Wolf et al does not disclose deactivation of the negative regulatory region and active DNA binding nor does Wolf et al disclose the addition of unique C-terminal regions.

With regard to Arai et al, applicant argues while Arai et al discloses the loss of binding to pAb421 and pAb122, there is no disclosure or suggestion of the loss of the negative regulatory domain or the gain of an antibody binding region.

These arguments have been considered but are not found to be persuasive. Wolf et al and Arai et al will be discussed together because both references are drawn to the same disclosed composition, the plasmid pM8. The p53as molecule encoded by this plasmid, just as the p53as molecule disclosed in the specification, is truncated by 9 C-terminal amino acids and has gained the disclosed unique regions of intron 10. The molecule has lost the pAb421 binding site, which Hupp et al (IDS) teaches is coincident with the negative regulatory domain and is lost when the regulatory domain is lost, thus indicating loss of the negative regulatory region by the molecule in plasmid pM8. Wolf et al and Arai et al are silent with regard to binding by antibodies to the unique intron 10 sequences. Wolf et al and Arai et al also do not perform DNA binding assays with their composition, however, it would appear that the composition of Wolf et al and Arai et al is identical to alternatively spliced p53 with the same changes to the C-terminus, i.e. 9 amino acid truncation and intron 10 addition. It certainly differs from active p53 in the 50 amino acids of the C-terminus. With regard to antibody reactivity and DNA binding, the identity of the molecule would indicate that these features are inherent properties of the composition of Wolf et al and Arai et al. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the

absence of evidence to the contrary, the burden is upon the applicant to prove that the p53as molecules are functionally different than those taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

15. The rejection of Claims 1, 3, 4 and 15 under 35 U.S.C. 102(b) as being anticipated by Han et al (IDS; Nuc.Acids Res. 20:1979-1981, 1992) is maintained.

Applicant argues that Han et al do not incorporate the p53as cDNA into a vector and they do not produce protein let alone one that has a unique epitope. Applicant also argues that the rejection is at odds with the previous rejection under 112 first.

These arguments have been considered but are not found to be persuasive. Han et al do incorporate the p53as cDNA into a vector, either pGEM3z or pBluescript (see page 1980). Han et al disclose a p53as cDNA, in a plasmid, which is different in the 50 C-terminal amino acids and has unique intron 10 sequences identical to the instantly disclosed p53as molecules as acknowledged by the instant specification on page 1, line 3). Han et al do not express protein and do not study the resultant proteins ability to bind DNA or to bind antibody, however, the claims are not drawn to a protein, they are drawn to a plasmid which encodes a protein, i.e. they are drawn to DNA, identical to that disclosed by Han et al. Han et al are silent with regard to functional properties of the encoded protein, however, given the identity of the truncation and addition of sequence, the ability to bind DNA and to bind antibody would be an inherent property of the encoded protein. The office does not have the facilities for examining and comparing

applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the compositions are functionally different than those taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

With regard to the relevance of the 112 first rejection in light of the rejections over the art, applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The compositions of the art meet and are an embodiment of the required limitations of the claims. In contrast, the specification of a patent must teach those skilled in the art how to make and use **the full scope** of the claimed invention without "undue experimentation." Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444; Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification).

16. The rejection of Claims 5, 6, and 8-11 under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (Mol. Cell Biol. 5:127-132, 1985), Han et al (Nuc.Acids Res. 20:1979-1981, 1992), or Arai et al (Mol. Cell Biol. 6:3232-3239, 1986) in view of Lee et al (IDS; EP 529160) is maintained.

Applicant argues that none of cited references teaches to produce p53as in a viral vector in insect cells and that to combine said references is impermissible hindsight.

These arguments have been considered but are not found to be persuasive. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). Futher, it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art *In re Keller,* 642 F.2d 413, 288 USPQ 871 9ccpa 1981). In response to Applicants' argument that the Examiners conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicants' disclosure, such a reconstruction is proper, In re McLaughlin, 443 F.2d 1392; 170 USPQ 209 (CCPA 1971).

In the instant case, plasmid constructs of the p53as molecule were known in the art. Lee et al was cited to demonstrate that cloning of known sequences into baculoviral vectors was art standard technology and desirable for production of protein.

Therefore, it is maintained that it would have been *prima facie* obvious to and one of ordinary skill in the art would have been motivated to clone the sequences of Wolf et al, Han et al, or Arai et al into baculovirus vectors using the art standard technology disclosed by Lee et al with a reasonable expectation of success because Lee et al teach that cloning into baculovirus is desirable for production of protein.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lila Feisee
Supervisory Patent Examiner
Group 1800

Yvonne Eyler, Ph.D.
October 8, 1997